Lung transplantation for emphysema: Impact of age on short- and long-term survival

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Abstract: OBJECTIVES: Overall, emphysema (EMP) is the most common indication for lung transplantation. The majority of patients present with chronic obstructive pulmonary disease (COPD) and less frequently with alpha-1 antitrypsin deficiency (A1ATD). We analysed the results of lung transplants performed for EMP in order to identify the impact of age on short- and long-term outcome. METHODS: A retrospective analysis was undertaken of the 108 consecutive lung transplants for EMP performed at our institution from November 1992 to August 2013 (77 COPD, 31 A1ATD). Retransplantations were excluded. RESULTS: The median age was 56 years (range 31-68). Thirty-day mortality rate was 3.7%. One- and 5-year survival rates in COPD and A1ATD recipients were comparable (P = 0.8). The 1- and 5-year survival rates for recipients aged <60 years old were significantly better than the age group of 60 years (91 and 79 vs 84 and 54%, P = 0.05). Since 2007, the 1- and 5-year survival for these two age groups were 96 and 92 vs 86 and 44%, respectively, P = 0.04, log-rank test). For the following parameters, we were not able to find any difference to affect survival rates: use of intraoperative extracorporeal membrane oxygenation, waiting list time, sex, graft size reduction, body mass index and diagnosis. In multivariate analysis, age at transplantation (60 years old) (HR 2.854; 95% confidence interval (CI) 1.338-6.08, P = 0.008) and unilateral lung transplantation (HR 15.2; 95% CI 3.2-71.9, P = 0.009) were independent risk factors for mortality. CONCLUSIONS: COPD and A1ATD recipients have similar overall long-term survival. Recipients aged 60 years and unilateral lung transplants were risk factors for mortality.

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Lung transplantation for emphysema: impact of age on short- and long-term survival†

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Abstract

OBJECTIVES: Overall, emphysema (EMP) is the most common indication for lung transplantation. The majority of patients present with chronic obstructive pulmonary disease (COPD) and less frequently with alpha-1 antitrypsin deficiency (A1ATD). We analysed the results of lung transplants performed for EMP in order to identify the impact of age on short- and long-term outcome.

METHODS: A retrospective analysis was undertaken of the 108 consecutive lung transplants for EMP performed at our institution from November 1992 to August 2013 (77 COPD, 31 A1ATD). Retransplantations were excluded.

RESULTS: The median age was 56 years (range 31–68). Thirty-day mortality rate was 3.7%. One- and 5-year survival rates in COPD and A1ATD recipients were comparable ($P = 0.8$). The 1- and 5-year survival rates for recipients aged <60 years old were significantly better than the age group of ≥60 years (91 and 79 vs 84 and 54%, $P = 0.05$). Since 2007, the 1- and 5-year survival for these two age groups were 96 and 92 vs 86 and 44%, respectively, $P = 0.04$, log-rank test). For the following parameters, we were not able to find any difference to affect survival rates: use of intraoperative extracorporeal membrane oxygenation, waiting list time, sex, graft size reduction, body mass index and diagnosis. In multivariate analysis, age at transplantation (≥60 years old) (HR 2.854; 95% confidence interval (CI) 1.338–6.08, $P = 0.008$) and unilateral lung transplantation (HR 15.2; 95% CI 3.2–71.9, $P = 0.009$) were independent risk factors for mortality.

CONCLUSIONS: COPD and A1ATD recipients have similar overall long-term survival. Recipients aged ≥60 years and unilateral lung transplants were risk factors for mortality.

Keywords: Emphysema • Lung transplantation • Morbidity • Age • Mortality • Survival

INTRODUCTION

Chronic obstructive pulmonary disease [COPD, emphysema (EMP) related to smoking] is overall the most common indication for adult lung transplantation [1]. If we include EMP related to alpha 1-antitrypsin deficiency (A1ATD), the proportion increases to 40% of all lung transplants performed worldwide [1]. Although more than 14 000 lung transplants were performed till June 2012, there are still questions regarding the appropriate timing of the procedure in the natural history of EMP, the type of procedure and aspects of quality of life [1, 2].

The currently accepted recommendations for the timing of referral for lung transplantation are based on an expected survival benefit, which means that post-transplant survival should exceed expected survival without transplantation [3, 4]. Survival benefit of lung transplantation, particularly in patients with cystic fibrosis, idiopathic pulmonary fibrosis and primary pulmonary hypertension has been reported [5]. Although the studies demonstrated survival benefit of transplantation for EMP, there are also studies that did not show any survival benefit for EMP [6, 7].

Most of the studies focused on the type of procedure (unilateral versus bilateral) and/or type of the diagnosis namely COPD versus A1ATD [3, 8–13]. In the present study, we analysed the results of lung transplants performed for EMP in order to identify the impact of age on short- and long-term outcome.

MATERIALS AND METHODS

We performed a retrospective review of prospectively collected data of 108 recipients undergoing lung transplantation for EMP from November 1992 to August 2013 at the University Hospital Zurich. The diagnosis was COPD in 77 and A1TTD in 31 recipients.

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Retransplantations were excluded. Sensor date for survival analysis was 3 November 2013. Follow-up was complete in all patients with a median of 36 months [interquartile range (IQR), 14–100].

Data analysis

Statistical analysis was performed using the Statistical Package for the Social Science, IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables are shown as median (IQR). Kaplan–Meier analysis was used to calculate actuarial survival. The log-rank test was used to test the difference in Kaplan–Meier survival curve between the groups. Cox regression method was used for multivariate analysis. A *P*-value less than 0.05 was considered the threshold value for statistical significance.

RESULTS

Patient characteristics and perioperative data are given in Table 1. Lung volume reduction surgery (LVRS) prior to transplantation was performed in 45 cases (42%), 34 in COPD and 11 in A1ATD.

Forced expiratory volume in one second (FEV1) at 1 year was 2.83 l (% predicted 95%) (IQR, 1.3 l). FEV1 at 5-year was 2.46 l (% predicted 81%) (IQR, 1.59 l)

For the whole group (*n* = 108), 45 patients underwent LVRS and 63 did not receive LVRS before lung transplantation. One-year survival for recipients who underwent LVRS was 91 versus 87% for those who did not receive LVRS before lung transplantation (*P* = 0.4, long-rank test). If we take the era since 2007 (*n* = 51), 1-year survival for recipients who underwent LVRS (*n* = 26) was 96 versus 87% for those who did not receive LVRS (*n* = 25) before lung transplantation (*P* = 0.7, long-rank test). Thirty-day mortality between these patients (2 deaths in each group) was comparable (*P* = 0.7).

At 1-year post-transplant, 64% (7/11) were free of Chronic Lung Allograft Dysfunction (CLAD) in unilateral transplanted patients, 9% (1 patient) had CLAD and 27% (3 patients) were deceased. At 5-year post-transplant, 54% of unilateral transplanted patients were free of CLAD and 45% had died (all-cause mortality). None of the patients ≥60 underwent unilateral lung transplantation.

At 1-year post-transplant, 84% (81/96) of the bilateral transplanted patients were free of CLAD, 4% (4 patients) had CLAD and 12% (11 patients) were deceased (all-cause mortality). In patients ≥60 who underwent bilateral lung transplantation (BLT), 23 were free of CLAD, 3 had CLAD. Five patients died (only 1 due to CLAD) in this age group. This means that 75% of CLAD (3/4) and 45% (5/11) of deaths occurred in the older COPD recipients (≥60 years old)

At 5-year post-transplant, 39% (27/69) of bilateral transplanted patients were free of CLAD, 26% (18 patients) had CLAD and 35% (24 patients) were deceased (all-cause mortality). Twenty-seven patients were alive but had not yet reached the 5-year time-point. For the age group ≥60 years, 4 were free of CLAD and 4 had CLAD. Twelve patients died in this group at 5 years. This means that 22% of CLAD (4/18) and 50% (12/24) of deaths occurred in older COPD patients (≥60 years old). This contribution of the elderly to the frequency of CLAD and mortality needs to be viewed in the light of the fact that only 30% of patients (32/107) belonged to the group transplanted at age ≥60.

Postoperative complications are given in Table 2. Thirty-day mortality rate was 3.7%.

One- and 5-year survival rates in COPD and A1ATD recipients were comparable (*P* = 0.8, log-rank test).

The 1- and 5-year survival rates for recipients aged <60 years were significantly better than the age group of ≥60 years old (91 and 79 vs 84 and 54%, *P* = 0.05, log-rank test). Since 2007, 1- and 5-year survival for these two age groups were 96 and 92 versus 86 and 44%, respectively, *P* = 0.04, log-rank test) (Fig. 1).

Applying univariate analysis, use of intraoperative extracorporeal membrane oxygenation, waiting list time, sex, size reduction, body mass index and diagnosis were not found to influence mortality (Table 3). Age at transplantation (≥60 years old) and unilateral lung transplantation were found to be risk factors for mortality (Table 4).

As seen in Table 5, none of the patients older than 60 years had undergone unilateral lung transplantation excluding the problems that might have been associated with morbidity and mortality.

Table 1: Perioperative patient characteristics

COPD	*n* = 78 (72%)
A1ATD	*n* = 30 (28%)
Female/male	*n* = 50/58
Age (years)	56 (51–60)
Preoperative FEV1 (l)	0.6 (0.52–0.86)
BMI (kg/m^2)	21 (19–24)
Waiting list time (days)	165 (67–286)
Donor variables	
Female/male	*n* = 37/71
Age (years)	50 (37–57)
PaO_2/FiO_2 (kPa)	43 (26–56)
Perioperative data	
Bridge to LuTx on ECMO	*n* = 3
Bridge to LuTx on MV	*n* = 1
Intraoperative ECMO/CPB	*n* = 22 (20%)
Unilateral LuTx	*n* = 11 (10%)
Bilateral LuTx	*n* = 97 (90%)
Lobar LuTx	*n* = 18
CIT (right) (min)	215 (179–273)
CIT (left) (min)	314 (260–375)
Total operation time (min)	372 (300–436)
ICU time (days)	4 (2–7)
FEV1 at discharge (l)	2.3 (1.7–2.7)

Data are presented as number (%) or median (interquartile range). COPD: chronic obstructive pulmonary disease; A1ATD: alpha-1 antitrypsin deficiency; BMI: body mass index; l: litre; FEV1: forced expiratory volume in one second; kPa: kilopascal (1 kPa = 7.5 mmHg), ECMO: extracorporeal membrane oxygenation; MV: mechanical ventilation; CBP: cardiopulmonary bypass; LuTx: lung transplantation; CIT: cold ischaemic time; min: minutes; ICU: intensive care unit.

Table 2: Postoperative complications (*n*)

Tracheotomy	11
Haemothorax (<10 days)	7
Haemothorax (>10 days)	6
Pneumothorax	9
Late pleural effusion	3
PGD (Grade 2–3, T48/72)	6
Lymphocele	5
Phrenic nerve injury	1
Thoracic hernia	1
Technical complications	6
Abdominal complications	15

PGD: primary graft dysfunction; *n*, number.

DISCUSSION

According to the recent International Society for Heart and Lung Transplantation (ISHLT) Registry Report, 14 784 lung transplants were performed for EMP (n = 12 602) and A1ATD (n = 2182) [1].

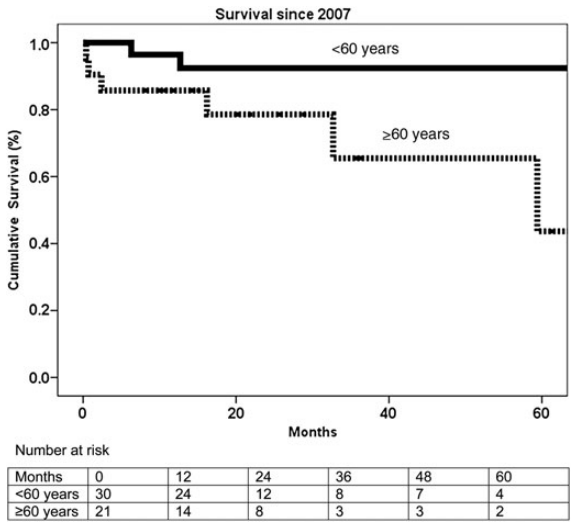

Figure 1: Survival by two age groups (<60 years old versus 60 years old) for patients with emphysema who underwent lung transplantation since 2007. The 1- and 5-year survival for these two age groups were 96 and 92 versus 86 and 44%, respectively, P = 0.04 (log-rank test).

Single lung transplantation (SLT) was performed in 49.8%, and BLT in 33%. Between 1997 and 2001, only ∼28% of transplants performed for EMP were BLTs. Thereafter, beginning with 2013, the number of BLTs increased steadily reaching 72% in 2011 [1]. The ISHLT Registry reports a 6.9 years of median survival in recipients that received BLT compared with 4.6 years in SLT recipients [1]. These rates increase to 9.6 years in BLT recipients and 6.5 years in SLT recipients who survive the first year following transplantation [1].

BLT is preferred by the most centres, as native lung hyperinflation post-SLT might be responsible for the inferior results of SLTs [14, 15]. However, SLT has shorter total ischaemia and operation time resulting in lower perioperative morbidity and mortality rates [16]. Other reasons for supporting SLT are reduction of the donor organ shortage and decreased waiting list morbidity and mortality [16].

In a retrospective study, Sundaresan *et al.* [9] reported that recipients who underwent BLT or SLT had comparable morbidity and mortality rates. In this series, overall hospital mortality was 6.2% [9]. The authors did not find any difference in hospital stay, intensive care unit stay or duration of mechanical ventilation between BLT and SLT recipients. However, 5-year survival in BLT recipients was 53% compared with 41% in SLT recipients [9]. In another study, Cassivi *et al.* [10] reported a 5-year survival rate of 66.7% in BLT and 44.9% in SLT recipients, respectively. On the other hand, Delgado *et al.* from Spain demonstrated comparable 5-year survival rates, 59% for SLT and 56% for BLT. The frequency of bronchiolitis obliterans syndrome was 34% in SLT and 42% in BLT [11].

Thabut *et al.* [12] compared survival after both SLT and BLT in EMP patients by analysing data from ISHLT Registry data. The

Table 3: Univariate analysis showing hazard of death following lung transplantation in emphysema recipients (n = 108)

Variable	Coefficient	Standard error	Hazard ratio	95% CI Lower	95% CI Upper	P-value
Sex	−0.438	0.332	0.645	0.336	1.238	0.187
Waiting List time	0.000	0.001	1	0.998	1.001	0.649
Size reduction	0.133	0.477	1.143	0.449	2.908	0.78
Diagnosis[a]	0.126	0.372	1.134	0.547	2.354	0.735
BMI	0.016	0.037	1.016	0.945	1.092	0.6
ECMO use[b]	0.477	0.425	1.612	0.701	3.707	0.261
Age group[c]	1.127	0.399	3.085	1.413	6.739	0.005
Unilateral LuTx	3.553	0.919	34.932	5.764	211.68	0.000

BMI: body mass index; CI: confidence interval; ECMO: extracorporeal membrane oxygenation; LuTx: lung transplantation.
[a]COPD versus A1ATD.
[b]Intraoperative ECMO or cardiopulmonary bypass use.
[c]≥60 years old.

Table 4: Multivariate analysis for hazard of death following lung transplantation in emphysema recipients (n = 108)

Variable	Coefficient	Standard error	Hazard ratio	95% CI Lower	95% CI Upper	P-value
ECMO use[a]	0.5	0.43	1.652	0.71	3.839	0.24
Age group[b]	1.04	0.386	2.854	1.338	6.088	0.008
Unilateral LuTx	2.725	0.792	15.249	3.231	71.967	0.009

BMI: body mass index; CI: confidence interval; ECMO: extracorporeal membrane oxygenation; LuTx: lung transplantation.
[a]Intraoperative ECMO or cardiopulmonary bypass use.
[b]≥60 years old.

Table 5: Cause of death in emphysema recipients undergoing lung transplantation shown for the two age groups

Cause of death (n = 50)	Age at LuTx		Total
	<60 years	≥60 years	
Respiratory infection	6 (1)[a]	4	10
Gastrointestinal perforation or haemorrhage	6	3	9
Multiorgan failure	4 (2)	3	7
Allograft dysfunction/failure	6 (3)	1	7
Kidney failure	3 (1)	1	4
Cerebral infarction or haemorrhage	3	1	4
Malignancy	3 (2)		3
Cardiac failure		2	2
Sepsis	2 (1)		2
Unknown	1 (1)	1	2

LuTx: lung transplantation.
[a]Numbers in parenthesis indicate unilateral lung transplantation.

median survival after either type of lung transplants for patients with EMP was 5.0 years. The proportion of patients who had BLT increased from 22% in 1993 to 56% in 2006. Median survival time after BLT was longer than after SLT. However, BLT had little benefit compared with SLT for patients who were ≥60 years old. These authors concluded that BLT leads to longer survival than SLT in patients with EMP, especially those who are <60 years old [12].

Meyer *et al.* [13] analysed 2260 lung transplant recipients with EMP recorded in the ISHLT/United Network for Organ Sharing Thoracic Registry between January 1991 and December 1997. The multivariate model showed a higher risk ratio for mortality in patients aged 40–57 years who received SLT versus BLT. They concluded that SLT might offer acceptable early survival rates for patients with end-stage respiratory failure. However, long-term survival data favour BLT in younger recipients until approximately 60 years old. Their reported data suggest that a BLT approach offers a significant survival advantage to recipients younger than 60 years old [13].

The superiority of BLT over SLT has also been shown in a multicentre study [17]. From these studies, it can be concluded that BLT has similar short-term results compared with SLT, but superior intermediate and long-term results [18].

Other than the survival advantage shown in prior studies, there are other facts for performing BLT in patients with EMP [18]. Hyperinflation of the native lung was reported to occur in 5–15% of patients after SLT, sometimes requiring LVRS [19–21]. Pneumonia in the native lung occurs in 10–20% of patients, and with a mortality rate up to 20% of those patients who develop this complication [22, 23]. Development of lung cancer in the native lung was reported to be ∼2–3% of patients [24].

On the other hand, Hadjiliadis and Angel [18] reported that SLT might be beneficial for patients with EMP if they develop severe primary graft dysfunction. These patients might still have a functioning emphysematous lung that could potentially sustain patients while primary graft dysfunction resolves [18].

In conclusion, our data show that recipients aged ≥60 years old and unilateral lung transplants were risk factors for mortality. Patients younger than 60 years old should be offered BLT in order to achieve survival benefit for EMP recipients.

Conflict of interest: none declared.

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